AMENDMENTS TO THE DRAWINGS:

The attached drawing sheets include changes to FIG. 1. A new drawing sheet has been submitted for FIG. 2. These sheets replace the original drawing sheets for FIG. 1 and FIG. 2.

As requested by the Office, FIG. 1 has been corrected to properly label the drawing "FIG. 1."

REMARKS

Applicants respectfully request reconsideration and allowance of all pending claims.

I. Amendments to the Specification

The requested amendments to the specification correct obvious typographical errors.

With regard to the requested amendment to the paragraph at page 14, lines 8-11, the μM unit in 76 μM and 65 μM would have been obvious to the person of ordinary skill as being derived from the Lineweaver-Burke chart shown in FIG. 1. It is known to the person of ordinary skill that the values of K_i and K_m can be calculated from the Lineweaver-Burke chart. These values are derived from the negative inverse of the x-intercept, i.e., where the lines cross the x-axis. Accordingly, it would have been obvious to the person of ordinary skill that the proper units for the values of K_i and K_m are both μM.

II. Status of the Claims

Upon entry of this amendment, claims 1-3, 5, 6 and 9-11 remain pending in the application.

Claim 2 has been withdrawn as being drawn to a non-elected invention.

Claims 3, 5, and 6 have been amended.

Support for the amendment to the R definition in claim 1 can be found at, for example page 8, line 8, wherein R can be phenyl (an aromatic ring) or pyridyl (a heteroaromatic ring). Further support can be found at page 8, line 31 to page 9, line 1.

Support for the amendment to claim 3 can be found in original claim 1.

III. Priority

A certified copy of the EPO priority document, EPO Patent Application Number 02078228.0, has been ordered and will be provided as soon as possible.

IV. Specification

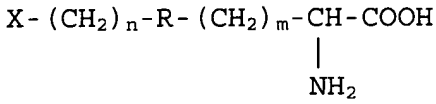
The requested amendments to the specification are in response to the objections stated on page 4 of the Office Action. Accordingly, applicants request withdrawal of the objections.

Additionally, applicants submit herewith corrected replacement FIG. 1 and a replacement FIG. 2.

V. Claim Rejections Under 35 U.S.C. §102(b)

Reconsideration is requested of the rejection of claims 1 and 3 as being anticipated by Wester et al., THE JOURNAL OF NUCLEAR MEDICINE, **1999**, 40(1), 205-212.

Claim 1 is directed to a halogenated amino acid analogue having the general formula:



wherein:

X is a radioactive halogen;

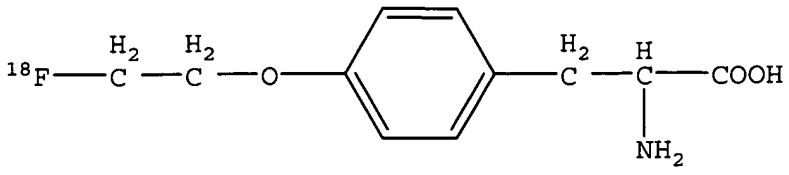
m is 0 or 1;

n is 0, 1, 2, 3, 4, 5, or 6;

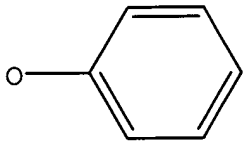
R is (C_1 - C_6) alkyl optionally substituted with thioether or ether oxygen atom when n is 0; and

R is an aromatic ring, a heteroaromatic ring, or substituted aromatic or heteroaromatic ring when n is 1, 2, 3, 4, 5 or 6.

The Wester et al. reference is cited for disclosing O-(2-[^{18}F]fluoroethyl-L-Tyrosine, which has the structure:



. This compound is referred to as ^{18}F-FET in applicants' specification. See page 3, lines 5-6 of applicants' specification. The Office asserted that the Wester et al. compound anticipates the



structure as defined by claim 1 when R is and $X-(CH_2)_n-$ is bonded to the oxygen atom on the R group.

The Wester et al. compound does not anticipate applicants' halogenated amino acid analogues as defined by claim 1. In applicants' specification, applicants distinguished their halogenated amino acid analogues in which R is an aromatic ring, a heteroaromatic ring, or a "substituted aromatic or heteroaromatic ring" from ^{18}F-FET as disclosed in Wester et al. See page 4, lines 15-30 where applicants first discuss Wester et al.'s ^{18}F-FET and then explain that their invention is "based on the new approach to introduce ***an alkyl side chain on the phenyl ring*** to facilitate introduction of the radioactive atom." Moreover, "[t]his reduces the labelling chemistry to direct conventional nucleophilic aliphatic substitution ***on the alkylphenylic side branch*** of the L-amino acid." In other words, applicants claimed halogenated amino acid analogues wherein R is an aromatic ring, a heteroaromatic ring, or a substituted aromatic or heteroaromatic ring include only those analogues in which the alkyl halide group ($X-(CH_2)_n-$) is substituted directly on the aromatic or heteroaromatic ring rather than substituted on a substituent (-O-) already present on the ring as in Wester et al.'s ^{18}F-FET.

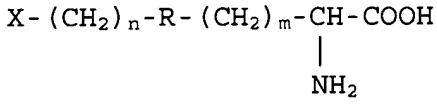
The remainder of applicants' specification is internally consistent with this meaning. For example, see page 6, lines 1-6 and page 9, lines 8-14 where applicant describes

derivatization of the 2, 3, 4, and 5 positions on aromatic rings. See also page 8, lines 13-15, where applicants' state "the ***substitution*** of an alkyl group, provided with an appropriate leaving group, ***on the phenyl ring of an aromatic amino acid***... ."

Furthermore, claim 3 is also consistent with this meaning. Claim 3 further limits R to phenyl, hydroxyphenyl, pyridyl, or hydroxypyridyl which are within the definition of an aromatic ring, a substituted aromatic ring, a heteroaromatic ring, and a substituted heteroaromatic ring, respectively. Both hydroxyphenyl and hydroxypyridyl include a hydroxyl group substituted in place of a hydrogen on the phenyl or pyridyl ring. This is further evidence of the meaning of the term "substituted aromatic or heteroaromatic ring."

In view of the foregoing, claim 1 is not anticipated by Wester et al. because the reference does not disclose a halogenated amino acid analogue having an aromatic ring, a heteroaromatic ring, or a substituted aromatic or heteroaromatic ring within the meaning of claim 1. Accordingly, applicants request withdrawal of the rejection.

With regard to claim 3, it is directed to a halogenated amino acid analogue having the general formula:



wherein:

X is a radioactive halogen;

m is 0 or 1;

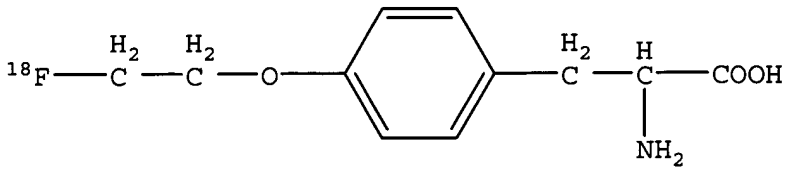
n is 0, 1, 2, 3, 4, 5, or 6;

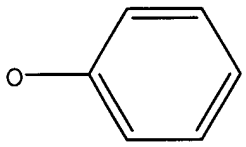
R is (C_1 - C_6) alkyl optionally substituted with thioether or ether oxygen atom when n is 0; and

R is phenyl, hydroxyphenyl, pyridyl, or hydroxypyridyl when n is 1, 2, 3, 4, 5 or 6.

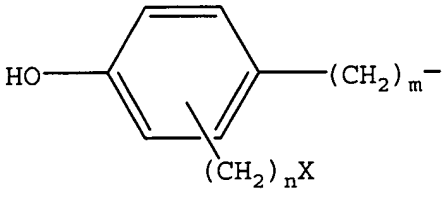
The Wester et al. reference is cited for disclosing O-(2-

[^{18}F]fluoroethyl-L-Tyrosine, which has the structure:

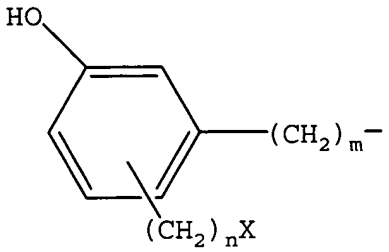


This compound does not anticipate applicants' halogenated amino acid analogues as defined by claim 3. The Office asserts that R in Wester et al.'s compound is  . Therefore, Wester's compound includes an ether linkage between the alkyl side chain and the phenyl ring.

In contrast, applicants' claimed formula does not define a halogenated amino acid analogue having an ether moiety. For example, where R is hydroxyphenyl, the structure comprises a phenol, i.e., an alcohol on an aromatic ring. The phenol may have the following exemplary structures:



and



The physical and chemical properties of ethers and alcohols are different from each other. For example, alcohols have a mildly acidic hydroxyl group, while ethers do not. Alcohols have both a hydrogen atom and an oxygen atom which can engage in hydrogen bonding, which typically raises the boiling point of alcohols for a given molecular weight. Ethers have only a sterically hindered oxygen atom, so they typically are characterized by

lower boiling points for a given molecular weight.

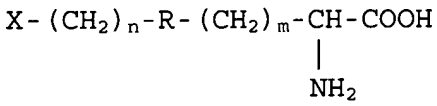
Accordingly, the Wester et al. reference does not disclose applicants' claimed analogues when R is hydroxyphenyl. Moreover, the Wester et al. reference does not disclose analogues in which R is phenyl, pyridyl, or hydroxypyridyl.

Since Wester et al. do not disclose any compounds having the structure defined in applicants' claim 3, it necessarily follows that the reference does not anticipate claim 3. Accordingly, applicants request withdrawal of the rejection.

VI. Claim Rejections Under 35 U.S.C. §103(a)

Reconsideration is requested of the rejection of claims 1, 3, 5-6, and 9-11 as being obvious over Wester et al. in view of Sheffer-Dee-Noor et al., TETRAHEDRON, **1994**, 50(23), 7009-7018.

Claim 1 is directed to a halogenated amino acid analogue having the general formula:



wherein:

X is a radioactive halogen;

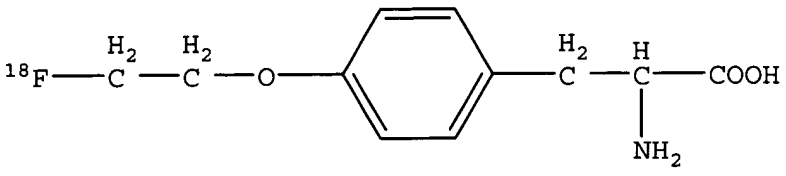
m is 0 or 1;

n is 0, 1, 2, 3, 4, 5, or 6;

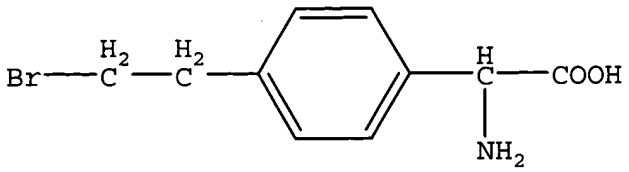
R is (C_1 - C_6) alkyl optionally substituted with thioether or ether oxygen atom when n is 0; and

R is an aromatic ring, a heteroaromatic ring, or a substituted aromatic or heteroaromatic ring when n is 1, 2, 3, 4, 5 or 6.

The Wester et al. reference is cited for disclosing O-(2-[^{18}F]fluoroethyl-L-Tyrosine, which has the structure:



The Sheffer-Dee-Noor et al. reference is cited for disclosing p-(2-bromoethyl)phenylglycine, which has the structure:



The Office asserts that "[o]ne skilled in the art would have found the claimed compounds...defined in claim 1 with prima facie obvious [sic] because it is suggested by combined [sic] the two prior arts as described previously. The motivation to make the claimed compounds derives from the expectation that the claimed compounds...are used as tracers in PET..."

According to the MPEP,

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. MPEP §2143, first paragraph.

In this case, the combination of references does not render applicants' claim 1 obvious because there is no motivation to combine the references in the manner suggested by the Office.

The Wester et al. reference is directed to a method for preparing radioactive tracers for use in tumor imaging. An essential component of radioactive tracers is a compound having a radioactive element, in this case, ^{18}F. The Sheffer-Dee-Noor et al. reference is in the disparate field of providing phenylglycine type amino acids, which "have found application in the synthesis of semisynthetic β-lactam antibiotics." See page 7009, 1st paragraph of Sheffer-Dee-Noor et al. The compounds described by Sheffer-Dee-Noor et al. do not contain radioactive halogen, and the reference does not provide any motivation to synthesize these compounds with radioactive halogen because there is no suggestion in the reference that synthesizing phenylglycine amino acids with radioactive halogen

is useful in the "synthesis of semisynthetic β-lactam antibiotics."

Moreover, radioactive tracers for use in tumor imaging must fulfill certain requirements. For example, the tracer should be amenable to accumulation in the tumor. See applicants' specification at page 2, line 18 to page 3, line 11. Additionally, the tracers should not be subject to renal accumulation. See applicants' specification at page 3, lines 12-25. Finally, the tracers should "be easily and quickly synthesized and can thus also be labeled with F-18 which has a half-life of only 2 hours." See applicants' specification at page 4, lines 9-14.

There is no disclosure in Sheffer-Dee-Noor et al. that their phenylglycine compounds have any of these properties, i.e., specificity to the tumor, safety as shown by low renal accumulation, and quick synthesis to maintain radioactivity. Sheffer-Dee-Noor et al. merely state that their compounds are useful for synthesizing β-lactam antiobiotics, which is not at all related to the use of radioactive tracers in a pharmaceutical composition. One of ordinary skill in the art would not have looked to the Sheffer-Dee-Noor et al. reference for preparing compounds used as tracers in PET.

Also, the rejection does not indicate what suggestion or motivation that one of ordinary skill in the art would have derived from this reference to modify the compounds described by Wester et al.

Accordingly, there is no motivation to make the compounds of claim 1 from the disclosures of Wester et al. and Sheffer-Dee-Noor et al. with the expectation that they are useful as tracers in PET. Since the combination of references fails to render claim 1 obvious, applicants request withdrawal of the rejection.

Claim 3 is patentable for substantially the same reasons described above in connection with claim 1.

Claims 5-6 and 9-11 depend from claim 1 and are therefore patentable for the same reasons as claim 1 and by virtue of the additional requirements therein.

With specific regard to claim 9, it discloses several species of radioactive halogenated amino acid analogues. The combination of references fails to render this claim obvious for the additional reason that neither reference discloses any of these compounds.

VII. Claim Rejections Under 35 U.S.C. §112

Reconsideration is requested of the rejection of claims 1, 3, 9 under 35 U.S.C. §112, first paragraph, for failing to comply with the written description requirement.

The Office asserts that:

> The specification discloses a general procedure for synthesis of [18F]fluorealkyl phenylalanine on page 9-14. However, the specification does not teach how to make other radio labeled compounds, and/or heteroaromatic ring containing compounds, such as pyridine-ring containing compound, as well as other claimed radio-labeled amino acid compounds...

Applicants respectfully disagree because the specification describes the synthesis of other radio labeled compounds in such a way as to reasonably convey that the inventors had possession of the claimed invention at the time of filing the application.

For example, applicants described a method for preparing ^{18}F-radio labeled Tyrosine. At page 9, line 28, applicants describe a suitable commercially available starting material, CH_3-O-L-2-I-Tyr for the synthesis of ^{18}F-radio labeled Tyrosine. The reaction sequence for preparing protected L-2-alkyltosyl-Tyrosine from another commercially available starting material, L-2-I-Tyr, is described at page 12 of applicants' specification from lines 19-21. Protected L-2-alkyltosyl-Tyrosine is a suitable pre-cursor for preparing ^{18}F-radio labeled Tyrosine. The person of ordinary skill in the art would also have known

that the reaction sequence for preparing ^{18}F-radio labeled Phenylalanine from L-2-tosylethyl-Phenylalanine described in Example 2 on page 13 of applicants' specification is applicable to preparing ^{18}F-radio labeled Tyrosine from protected L-2-alkyltosyl-Tyrosine.

Moreover, the person of ordinary skill in the art would have known that these reaction sequences further apply to preparing ^{18}F-radio labeled azatyrosine from suitable azatyrosine starting material.

Applicants additionally described a method for preparing ^{18}F-radio labeled Leucine. On page 12, lines 15-17 and 23-25, applicants disclose that protected Leucine can be brominated according to the method described in Example 1.1, which is found at page 11, lines 20-29. The ethyltosyl group may then be introduced according to the method described in Example 1.2, which is found at page 12, lines 5-13. Protected ethyltosyl-Leucine is a suitable pre-cursor for preparing ^{18}F-radio labeled Leucine. The person of ordinary skill in the art would also have known that the reaction sequence for preparing ^{18}F-radio labeled Phenylalanine from L-2-Tosethyl-Phenylalanine described in Example 2 on page 13 of applicants' specification is applicable to preparing ^{18}F-radio labeled Leucine from protected ethyltosyl-Leucine.

Moreover, the person of ordinary skill in the art would have known that these reaction sequences further apply to preparing ^{18}F-radio labeled Valine and Isoleucine from suitable starting material.

In view of the foregoing, applicants have sufficiently described the synthesis of other radio labeled compounds in such a way as to reasonably convey that the inventors had possession of the claimed invention. Accordingly, applicants request withdrawal of the rejection.

Reconsideration is requested of the rejection of claim 1 under 35 U.S.C. §112, second paragraph. The Office asserted

that the "term 'substituted' is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention." Applicants submit that the specification sufficiently describes what is meant by a "substituted" aromatic and heteroaromatic ring. For example, "substituted" aromatic and heteroaromatic rings include rings in which the substituent is the hydroxyl group defined in claim 3. This definition finds support in applicants' specification, for example, at page 5, lines 20-23 and page 5, line 29 to page 6, line 6.

Moreover, the term "substituted" in this specification is used in the context of amino acids. The person of ordinary skill in the art would reasonably understand that in this context, "substituted" may refer to any of the groups found on aromatic rings in common or even uncommon amino acids. For example, the person of ordinary skill would understand that an amino acid having a "substituted" aromatic ring may include tyrosine and meta-tyrosine, in which a phenyl ring is substituted with a hydroxyl group.

In view of the foregoing, the term "substituted" in claim 1 is supported by the description in the specification, and applicants request withdrawal of the rejection.

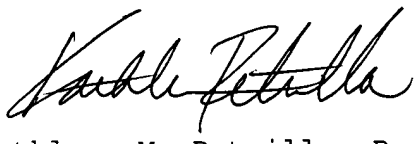
Reconsideration is requested of the rejection of claims 5 and 6. Claims 5 and 6 have been amended to properly depend from claim 1. Applicants request withdrawal of the rejection.

CONCLUSION

In view of the above, applicants respectfully request allowance of all of the pending claims.

Applicants do not believe that a fee is due in connection with this response. If, however, the Commissioner determines that a fee is due, he is authorized to charge Deposit Account No. 19-1345.

Respectfully submitted,



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